REMARKS

Claims 1-24 were pending in the application with Claims 21-24 withdrawn from consideration. Claims 1 and 14 have been amended. Upon entry of these amendments, Claims 1-20 will be pending and under active consideration with Claims 21-24 withdrawn from active consideration. Claims 1 and 14 are independent.

Applicants submit respectfully that the amendments presented herein are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter.

Claims 1 and 14 have been amended to point out more particularly and claim more distinctly that which Applicants regard as their invention by now reciting "isolated *single-cell* hepatic progenitors" and "capable of differentiating *when exposed to differentiation-inducing growth conditions*" (emphasis added). The amendment of Claims 1 and 14 finds support throughout the specification, particularly in the Examples section beginning on page 12 of the specification, for example at page 28, lines 20-21, which teach the preparation of a single-cell suspension for isolating human hepatic precursors, and sections 1.3-1.6, pages 19-24, which describe differentiation-inducing growth conditions.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

I. The Rejection Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Final Office Action, at pages 3-5, rejects Claims 1-20 as allegedly being anticipated by Sargiacomo *et al.* (*J. Hepat.*, 28:480-490, 1998)(hereinafter, "Sargiacomo"), as further evidenced by Haruna *et al.* (*Hepatology*, 23:476-481, 1996)(hereinafter, "Haruna"), under 35 U.S.C. § 102(b). The Final Office Action alleges that Sargiacomo teaches that cell preparations from intact fetal livers were seeded into polystyrene flasks and cultured. The Final Office Action alleges further that, since the fetal liver cell preparations taught in Sargiacomo are disclosed to be isolated from human fetal livers, as are the presently-claimed isolated and identified hepatic progenitor cells, the cell preparations of Sargiacomo will have inherently the same physical and biochemical properties as the presently-claimed isolated and identified hepatic progenitor cells. The Final Office Action draws the alleged conclusion, therefore, that Sargiacomo teaches the isolation and identification of bipotent liver progenitor cells isolated from fetal livers (page 4, bottom). Applicants traverse respectfully.

Applicants submit respectfully that Claims 1-20, as amended, are not anticipated by Sargiacomo because Sargiacomo does not disclose each and every element of those amended claims, either explicitly or inherently, as is required for a *prima facie* showing of anticipation under 35 U.S.C. § 102(b). In particular, Claim 1, as amended, is directed to a composition comprising isolated single-cell bipotent hepatic progenitors which express at least one intercellular adhesion molecule (ICAM) antigen and do not express major histocompability complex (MHC) class Ia antigen, in which the bipotent hepatic progenitors have a capacity to differentiate when exposed to differentiation-

inducing growth conditions. Despite the Final Office Action's allegation that Sargiacomo teaches the isolation and identification of bipotent liver progenitor cells isolated from fetal livers, Applicants submit respectfully that Sargiacomo does **not** teach or suggest isolated single-cell hepatic progenitors, nor does Sargiacomo teach or suggest the identification of liver progenitors capable of differentiation when exposed to differentiation-inducing growth conditions. Further, Applicants submit respectfully that the teachings of Haruna do not evidence Applicants' claimed inventions, nor would Haruna cure the deficiencies of Sargiacomo with respect to the presently claimed inventions.

Sargiacomo teaches a fetal liver culture system which allows morphogenetic interactions consistent with the development of hepatic function (see Background/Aims, page 480). Fundamental to Sargiacomo's method is that intact "multi-size spherical hepatic units" were seeded into culture medium, to begin the growth process, so that hepatic architecture would be present. The integrity of these hepatic units to the Sargiacomo method is indicated in the sentence bridging pages 483-484, which recites that "[A]ll the hepatic specimens used for preparing the human FLCC [Fetal Liver Cell Culture] were immediately checked for structural integrity by LM [Light Microscope]. In fact, Sargiacomo teaches at pages 480-481 that the use of intact, 3-dimensional cell clusters is a cure to deficiencies noted in the art of maintaining isolated hepatocytes in cell culture where the method includes "dissociation of cells from the tissue matrix in which reciprocal interactions are critical for the maintenance of a differentiated cellular state" (sentence bridging pages 480-481). Accordingly, and while not acquiescing in the argument that the cell clusters of Sargiacomo contain bipotent hepatic progenitors,

Applicants submit respectfully that Sargiacomo not only fails to teach the isolation of single-cell hepatic progenitors, but actually teaches away from single-cell culture methods.

Further, Applicants submit respectfully that Sargiacomo does not even indicate that bipotent hepatic progenitors exist within the cell cultures taught by Sargiacomo. Inasmuch as Sargiacomo begins cell culture with intact hepatic units, it seems likely that differentiated hepatocytes and biliary cell clusters were present in the initial cell culture. As Sargiacomo performed none of the tests taught by Applicants to identify the presence of bipotent hepatic progenitors in Sargiacomo's cell cultures, there is no way to know whether such progenitors are actually present. While the Final Office Action would suggest that Sargiacomo's cell preparation must inherently contain bipotent hepatic progenitors as described by Applicants, it is also possible that the bipotent progenitors are excluded from Sargiacomo's cell preparation in the early stages. The Final Office Action indicates that Haruna teaches that hepatic progenitors are present in fetal human liver, with the implication that the cells identified by Haruna would be present in Sargiacomo's cell culture. Without acquiescing in the allegation that Haruna's methods actually identify bipotent hepatic progenitors, Applicants submit respectfully that Haruna teaches immunoperoxidase staining of formalin-fixed paraffin sections of ***intact*** liver, not dissociated liver components as taught by Sargiacomo. Hence, Applicants submit respectfully that one cannot determine whether the cells identified by Haruna are present in the Sargiacomo cell preparation.

Furthermore, application of the Haruna identification methods to the cultures of Sargiacomo would not yield the bipotent hepatic progenitor cells of the present invention

having the ***capacity to differentiate***. Applicants' submit respectfully that, as one skilled in the art will immediately recognize, mammalian liver cells that have been subjected to formalin fixation, and that are subsequently contained within peroxidase-stained paraffin sections, are no longer viable. Hence, such cells are not capable of differentiation as required under Claims 1 and 14, as amended.

Applicant submits respectfully that the claims of the present invention, as amended, are not anticipated by Sargiacomo, which does not teach or suggest each and every element of the present claims, and that the rejection to Claims 1-20 under 35 U.S.C. § 102(b) has been overcome. Accordingly, Applicant requests respectfully that the rejection to Claims 1-20 under 35 U.S.C. § 102(b) be withdrawn.

II. Rejection Under 35 U.S.C. § 112, Second Paragraph

At pages 2-3 of the Final Office Action, Claims 14-20 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter regarded as the invention. The Final Office Action alleges that the language of Claim 14 is unclear in that the claim recites the expression "capable of" with regard to the present inventive cells' capacity to differentiate or proliferate. The Final Office Action alleges that this capability is a latent property, and that the conditions for a latent property must be defined clearly. Applicants traverse respectfully.

Without acquiescing in the propriety of rejection, and solely to advance prosecution of the present application, Claim 14, from which Claims 15-20 depend, is

amended herein to add the clarifying recitation, "bipotent hepatic progenitors have a capacity to differentiate *when exposed to differentiation-inducing growth conditions*" (emphasis added). Applicants submit respectfully that, in light of the teachings of the specification, the conditions under which the differentiation property of the claimed cells is obtained are clearly defined.

On this basis, Applicants suggest respectfully that the rejections have been overcome, and Applicants request respectfully that the 35 U.S.C. § 112, second paragraph, rejection of Claims 14-20 be withdrawn.

CONCLUSION

Applicants submit respectfully that the present application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicants believe there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,

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